AZADECALIN GLUCOCORTICOID RECEPTOR MODULATORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is a 371 of PCT/US05/00607 filed 01/10/2005 which claims the benefit of United States Provisional Patent Application No. 60/535,460, filed January 9, 2004, which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] In most species, including man, the physiological glucocorticoid is cortisol (hydrocortisone). Glucocorticoids are secreted in response to ACTH (corticotropin), which shows both circadian rhythm variation and elevations in response to stress and food. Cortisol levels are responsive within minutes to many physical and psychological stresses, including trauma, surgery, exercise, anxiety and depression. Cortisol is a steroid and acts by binding to an intracellular, glucocorticoid receptor (GR). In man, glucocorticoid receptors are present in two forms: a ligand-binding GR-alpha of 777 amino acids; and, a GR-beta isoform which differs in only the last fifteen amino acids. The two types of GR have high affinity for their specific ligands, and are considered to function through the same transduction pathways.

[0003] The biologic effects of cortisol, including those caused by hypercortisolemia, can be modulated at the GR level using receptor modulators, such as agonists, partial agonists and antagonists. Several different classes of agents are able to block the physiologic effects of GR-agonist binding. These antagonists include compositions which, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One such known GR antagonist, mifepristone, has been found to be an effective anti-glucocorticoid agent in humans (Bertagna (1984) *J. Clin. Endocrinol. Metab.* **59**:25). Mifepristone binds to the GR with high affinity, with a dissociation constant (K_d) of 10^{-9} M (Cadepond (1997) *Annu. Rev. Med.* **48**:129).

[0004] Patients with some forms of psychiatric illnesses have been found to have increased levels of cortisol (Krishnan (1992) *Prog. Neuro-Psychophannacol. & Biol. Psychiat.* **16**:913-920). For example, some depressed individuals can be responsive to treatments which block the effect of cortisol, as by administering GR antagonists (Van Look (1995) *Human Reproduction Update* 1:19-34). In one study, a patient with depression secondary to Cushing's Syndrome (hyperadrenocorticism) was responsive to a high dose, up to 1400 mg per day, of GR antagonist mifepristone (Nieman (1985) *J. Clin Endocrinol.*